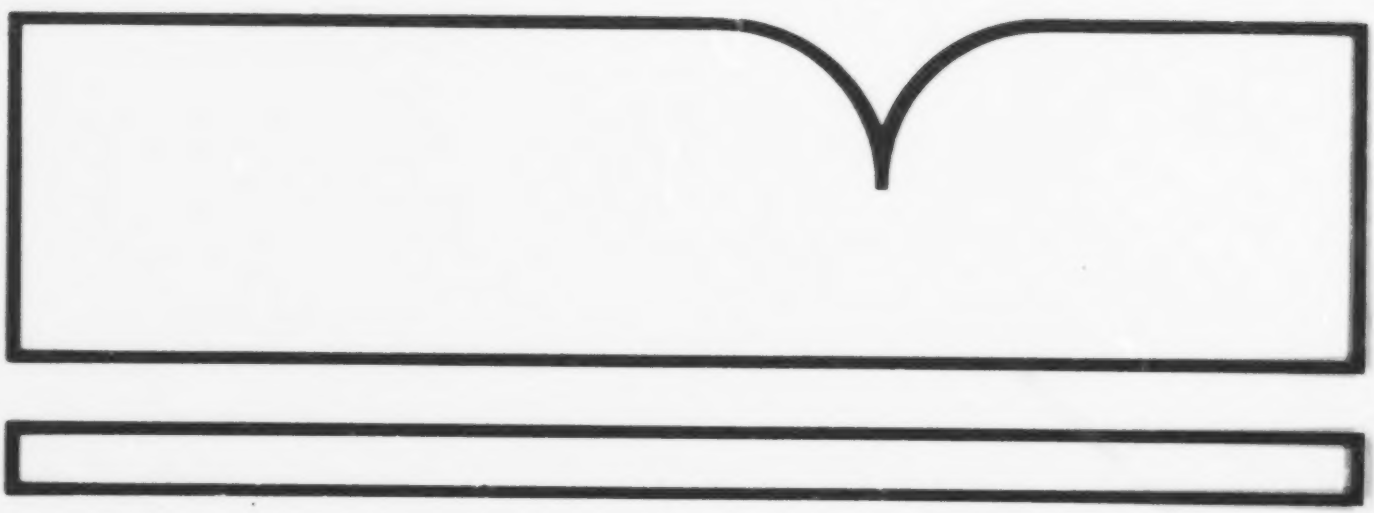
PB86-116415

Comparative Potency Method for Cancer Risk Assessment: Application to the Quantitative Assessment of the Contribution of Combustion Emissions to Lung Cancer Risk

(U.S.) Health Effects Research Lab.
Research Triangle Park, NC

Oct 85



U.S. Department of Commerce
National Technical Information Service
NTIS

EPA/600/D-85/238
October 1985

PB86-116415

Comparative Potency Method for Cancer Risk Assessment:

Application to the Quantitative Assessment of the Contribution of Combusiton Emissions to Lung Cancer Risk

by

Joellen Lewtas
Genetic Bioassay Branch
Genetic Toxicology Division
Health Effects Research Laboratory
Research Triangle Park, NC 27711

Health Effects Research Laboratory
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO.
EPA/600/D-85/238		PB86 116415/AS

4. TITLE AND SUBTITLE	5. REPORT DATE
COMPARATIVE POTENCY METHOD FOR CANCER RISK ASSESSMENT: Application to the Quantitative Assessment of the Contribution of Combustion Emissions to Lung Cancer Risk	October 1985
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) Joellen Lewtas	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS same as #12	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Health Effects Research Laboratory Office of Research and Development U.S. Environmental Protection Agency Research Triangle Park, NC 27711	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE EPA/600/11

15. SUPPLEMENTARY NOTES

16. ABSTRACT

Combustion sources emit soot particles containing carcinogenic polycyclic organic compounds which are mutagenic in short-term genetic bioassays in microbial and mammalian cells and are tumorigenic in animals. Although soot is considered to be a human carcinogen, soots from different combustion sources and fuels contain variable quantities of organic tars of somewhat different composition. This presents a serious problem when assessing risk since it is not possible to collect human cancer risk data for all the various possible exposures to combustion emissions. Furthermore it is impossible to collect human cancer data for exposures to emissions from new technologies which have not previously been in the environment. The use of chronic animal testing for each new combustion technology developed would be prohibitively expensive and time consuming. This problem has motivated us to develop and test a comparative potency risk assessment methodology which would utilize short-term mutagenesis and tumorigenesis data. This method was developed and tested using data from a battery of short-term mutagenesis bioassays, animal tumorigenicity data and human lung cancer risk estimations. This data base was developed for a series of complex mixtures including emissions from coke ovens, roofing tar pots, cigarette smoke, and automotive engines. The assumptions inherent in this method are discussed together with the methods and data base used to test these assumptions.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS *(This Report)*	21. NO. OF PAGES
RELEASE TO PUBLIC	UNCLASSIFIED	10
	20. SECURITY CLASS *(This page)*	22. PRICE
	UNCLASSIFIED	

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

COMPARATIVE POTENCY METHOD FOR CANCER RISK ASSESSMENT: APPLICATION TO THE QUANTITATIVE ASSESSMENT OF THE CONTRIBUTION OF COMBUSTION EMISSIONS TO LUNG CANCER RISK

Joellen Lewtas

Genetic Bioassay Branch, Genetic Toxicology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

Combustion sources emit soot particles containing carcinogenic polycyclic organic compounds which are mutagenic in short-term genetic bioassays in microbial and mammalian cells and are tumorigenic in animals (Lewtas, 1984; Holmberg and Ahlborg, 1983). Although soot is considered to be a human carcinogen (IARC, 1985), soots from different combustion sources and fuels contain variable quantities of organic tars of somewhat different composition. This presents a serious problem when assessing risk since it is not possible to collect human cancer risk data for all the various possible exposures to combustion emissions. Furthermore it is impossible to collect human cancer data for exposures to emissions from new technologies which have not previously been in the environment. The use of chronic animal testing for each new combustion technology developed would be prohibitively expensive and time consuming. This problem has motivated us to develop and test a comparative potency risk assessment methodology which would utilize short-term mutagenesis and tumorigenesis data.

A comparative potency method for cancer risk assessment has been developed based upon a constant relative potency hypothesis. This method was developed and tested using data from a battery of short-term mutagenesis bioassays, animal tumorigenicity data and human lung cancer risk estimations (Lewtas, 1981; Nesnow et al, 1982a,b; Albert et al, 1983; Lewtas et al, 1983). This data base was developed for a series of complex mixtures including emissions from coke ovens, roofing tar pots, cigarette smoke, and automotive engines. The series of automobiles used in this study

included both diesel- and gasoline-powered vehicles. The assumptions inherent in this method are discussed together with the methods and data base used to test these assumptions.

The comparative potency method for cancer risk assessment is based on the hypothesis that there is a constant relative potency between two different carcinogens across different bioassay systems (Lewtas, et al 1983). The mathematical expression for the constant relative potency model is the following:

$$\text{Relative Potency in Bioassay}_{(1)} = (k)\ \text{Relative Potency in Bioassay}_{(2)}$$

This assumption is implicit in any comparison which utilizes the relative toxicity of two substances in animals to determine which substance would most likely be less toxic to man. This constant relative potency assumption is a testable hypothesis, if the relative potency of two carcinogens in humans can be determined and compared to the relative potency in a series of in vitro and in vivo bioassays. The test of this model is whether there is a constant relationship (k) between the relative potencies in the two bioassays being compared such that:

$$\frac{\text{Relative Potency in Bioassay}_{(1)}}{\text{Relative Potency in Bioassay}_{(2)}} = \text{constant (k)}$$

This hypothesis was tested for three complex organic emissions from a coke oven, roofing tar pot, and cigarettes by using human lung cancer data from epidemiological studies of humans exposed to these emissions (Albert et al, 1983).

This method was initially applied to the estimation of a human life-time cancer risk (unit risk) for a series of diesel automobiles by comparison to the human cancer unit risk from coke oven, roofing tar, and cigarette according to the following equation (e.g., for coke oven emissions):

$$\text{relative human risk}\left(\frac{\text{diesel auto}}{\text{coke oven}}\right) = (k)\ \text{relative bioassay potency}\left(\frac{\text{diesel auto}}{\text{coke oven}}\right).$$

The relative potency in the mouse skin tumor initiation bioassay was directly used to estimate the cancer risk of diesel emissions. This approach to applying the comparative potency method assumes that when comparing between one of

the three human carcinogens and the automotive emissions, the mouse skin is directly proportional (k = 1) to the relative potency in humans. This assumption is supported by the correlation (r^2 = 0.96) between the relative potencies in mouse skin tumor initiating activity with the human lung cancer unit risks.

A series of diesel and gasoline automotive emissions, for which no human data were available, was also tested in the battery of in vivo and in vitro bioassays. The relative potency within the automotive samples across all these bioassays was, however, relatively constant. High correlations (r^2 = 0.72-0.95) were observed between the mutagenic activity of five automotive emissions (diesel and gasoline) and their tumor initiating activity (Lewtas, 1982). Since the relative mutagenic potency of these automotive emissions correlates so well with the relative tumorigenic activity, it is possible to calculate a proportionality constant to use in estimating the human risk to any one of these emissions from mutagenicity data. This calculation of k is also a test of the constant relative potency hypothesis. The relative potency constant ranged from 0.023 to 0.11 or approximately five-fold with the average k = 0.05.

The major assumption and main source of uncertainty in this comparative potency method is the validity of the constant relative potency hypothesis. Interspecies differences in absorption and metabolism, which present the most difficult problems in extrapolation from animals to humans, may also affect the relative carcinogenic potency. By developing and evaluating a comparative data base across human, animal, and short-term bioassays for the same substances, these assumptions can be tested. The constant relative potency model does not assume "a priori" that the carcinogens being compared are chemically similar. The coke oven, roofing tar, cigarette smoke, and automotive emission samples are similar in that they all contain polycyclic organic compounds which cause frameshift mutations in Salmonella typhimurium (Lewtas, 1984). These four emissions differed in their metabolic activation requirements (Claxton, 1981), and upon chemical fractionation and characterization significant differences were observed in the specific mutagenic/carcinogenic chemicals present (Lewtas, 1984). The similarity in chemical composition of the different diesel automobile emissions may however be the basis for the constant relative potency observed across the

short-term bioassays and animal tumorigenicity for this series of emissions. The mutagens and carcinogens present in these mixtures may differ only in their concentration.

Although pure compounds have been reported to range in carcinogenic and mutagenic potency over six orders of magnitude (Meselson and Russell, 1977), the relative potency of the extractable organics from soot collected from combustion emissions ranged from only a five-fold difference in the mouse skin tumorigenesis assay to a 150-fold difference in the mouse lymphoma gene mutation assay. The Ames Salmonella typhimurium mutagenesis assay showed approximately two orders of magnitude difference (100-110 fold) in mutagenic activity from the weakest to the most potent emission sample when measured per mass of extractable organics (e.g., rev/μg). The emission rates (rev/km or rev/J) for the particle-bound organics, however, differed in some cases by as much as five orders of magnitude (10^5). To directly compare the mutagenicity of emissions from various sources, it is critical to compare the rates of mutagenic emissions on the same basis (e.g., fuel consumption, distance driven, energy consumption, or yield). To compare rates of mutagenic emissions of mobile sources, we have compared the mutagenic activity per kilometer. These values range from a low of 0.05×10^5 revertants/km for a gasoline catalyst car to 5.2×10^5 rev/km for a diesel truck. The rates of mutagenic emissions from stationary sources are compared on the basis of fuel or energy consumption, and range from a low of 0.03×10^3 revertants/joule for a large coal fired power plant to a high of 660×10^3 rev/joule for an airtight wood stove.

This comparative potency method provides a framework for evaluating alternative energy sources, fuels, or control technologies by comparing them to the conventional technologies in short-term genetic bioassays. It is possible to extend the method described here for estimating lung cancer unit risks for diesel and gasoline automotive emissions to unit risk estimates for various combustion emissions or other complex mixtures through the data base established linking human, animal, and short-term genetic bioassay data. A simplified comparative approach to evaluating alternative energy sources is to employ parallel bioassay studies of the alternative (a) and conventional (c) source emissions and determine a relative risk by direct comparison as follows:

increased risk (a/c) = relative bioassay potency (a/c).

Since there is no one conventional standard petroleum-derived fuel or one standard combustion source, such studies need to consider the range of mutagenic and carcinogenic potency between different conventional sources and fuels. The establishment of such a range could then serve as a guide for evaluating alternative fuels or sources. For example, if the relative potency of the alternative source or fuel emissions fell within the range for the conventional fuels, one could assume no increased human risk. The battery of bioassays to be employed in such a study would depend upon availability of emission sample, resources, and time. As more bioassays are employed, however, confidence in the relative potency estimates should increase.

This direct comparative analysis of mutagenic emission rates provides a simple means of evaluating alternative energy sources. It is apparent from this data base that the organic emission rate (e.g., rev/kg fuel) may vary over a wider range than the mutagenicity or carcinogenicity of the emissions (e.g., rev/mg particles). Therefore, when directly comparing sources the mutagenic or tumorigenic emission rate should be compared.

The increased or decreased human cancer risk from combustion emissions may be of greater concern than the absolute risk from these emissions when we consider the effect of alternative energy technologies and fuels. The data of greatest value in determining this increased or decreased risk is comparative bioassay data on emissions from the complex mixture being evaluated or comparative bioassay data on the conventional and alternative technology being evaluated. Such studies should be useful in providing direction for engineers and chemists to design alternative energy sources and fuels which result in less mutagenic and potentially less carcinogenic emissions.

Quantitative risk assessment is fraught with many uncertainties. The validity of the assumptions underlying the risk model or method employed are often difficult to test or validate. Cancer risk assessment has generally employed either human epidemiological data from relatively high occupational exposures or animal cancer data from lifetime rodent bioassays. Low-dose extrapolation methods are often used with the human epidemiological data to estimate risks at lower environmental exposure levels. Scaling factors are used with animal data to extrapolate

from rodents to humans. The problems, controversies, and uncertainties associated with these methodologies have encouraged us to develop the concept and methodology for a comparative potency method for cancer risk assessment. This comparative potency method may be particularly appropriate for application to the quantitative cancer risk assessment of combustion emissions.

The comparative potency method for cancer risk assessment described in this paper cannot be employed without uncertainty or without invoking the constant relative potency hypothesis assumption inherent in the method. It is important to recognize that the assumptions and uncertainties in the compartive potency method are different from those invoked in either using low-dose extrapolation techniques with human data or scaling factors with animal data. This makes it possible, therefore, to perform quantitative cancer risk assessments with more than one approach with different methodological assumptions. It will be possible in the future to compare the quantitative risk assessments for one source using several independent cancer risk assessment methodologies.

DISCLAIMER

This paper has been reviewed by the Office of Research and Development, U.S. Environmental Protection Agency and has been approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the U.S. Environmental Protection Agency.

REFERENCES

Albert RE, Lewtas J, Nesnow S, Thorslund TW, Anderson E (1983). Comparative potency method for cancer risk assessment: Application to diesel particulate emissions. Risk Anal 3:101-117.

Claxton LD (1981). Mutagenic and carcinogenic potency of diesel and related environmental emissions: Salmonella bioassay. Environ Int 5:389-391.

Holmberg G, Ahlborg U (1983). Consensus report: Mutagenicity and carcinogenicity of car exhausts and coal combustion emissions. Environ Health Persp 47:1-30.

International Agency for Research on Cancer (1985). IARC

Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Polynuclear Aromatic Compounds, Part 4, Bitumous, Coal-Tars and Derived Products, Shale-Oils and Soots, Volume 35, Lyon, France: IARC.

Lewtas J, Bradow RL, Jungers RH, Harris BD, Zweidinger RB, Cushing KM, Gill BE, Albert RE (1981). Mutagenic and carcinogenic potency of extracts of diesel and related environmental emissions: Study design, sample generation, collection, and preparation. Environ Int 5:383-387.

Lewtas J (1982). Mutagenic activity of diesel emissions. In Lewtas J (ed): "Toxicological Effects of Emissions from Diesel Engines," New York: Elsevier Science Publishing Co., Inc., pp 243-264.

Lewtas J, Nesnow S, Albert RE (1983). A comparative potency method for cancer risk assessment: Clarification of the rationale, theoretical basis, and application to diesel particulate emissions. Risk Anal 3:133-137.

Lewtas J (1984). Combustion emissions: Characterization and comparison of their mutagenic and carcinogenic activity. In Stich HF (ed): "Carcinogens and Mutagens in the Environment, Vol IV," Boca Raton: CRC Press.

Meselson M, Russell K (1977). Comparisons of carcinogenic and mutagenic potency. In Hiatt HH, Watson JD, Winsten JA (eds): "Origins of Human Cancer, Book C," New York: Cold Spring Harbor Lab., pp. 1473-1481.

Nesnow S, Triplett L, Slaga TJ (1982a). Comparative tumor-initiating activity of complex mixtures on mouse skin. J Natl Cancer Inst 68:829-834.

Nesnow S, Evans C, Stead A, Creason J, Slaga TJ, Triplett LL (1982b). Skin carcinogenesis studies of emission extracts. In Lewtas J (ed): "Toxicological Effects of Emissions from Diesel Engines," New York: Elsevier Science Publishing Co., Inc., pp 295-320.